REMARKS

The Amendments

The Abstract has been amended to more clearly point out the claimed invention.

The amendment of claim 9 merely corrects a typographical error, and does not change the scope or patentability of the claim. Claim 25 is amended to incorporate a limitation from (now canceled) claim 26, and thus does not add new matter.

Rejections Under §102(b)

Claim 29 was rejected as anticipated under §102(b) over Elliot et al., US 4025510; over Elliot et al., J Heterocyclic Chem (1981) 189(4):799-800; and Elliot et al., J Org Chem (1980) 45(18):3677-81. Applicants submit that the rejections are moot after cancellation of claim 29.

Rejection under §112, First Paragraph

A. Claims 22-23

Claims 22 and 23 were rejected under §112, 1st paragraph, as not enabled for the full scope of the claim. Applicants appreciate the Examiner's recognition that the invention is enabled for the treatment of Crohn's disease, inflammatory bowel disease, rheumatoid arthritis, and chronic obstructive pulmonary disease, but respectfully traverse.

While it is true, as the Examiner points out, that arthritis in general can have many causes, the various forms of the disease are all grouped together under the label "arthritis" for a reason: they all share common features, such as pain, inflammation, and damage to the joints. The common features are mediated by TNFα, which is released as a result of the p38 MAP kinase cascade. As noted in the Examiner's reference (Brown et al., Bioorg Med Chem Lett (2004) 14:5383-87), "Inhibition of p38 kinase is thus an attractive approach to the treatment of **both pain and inflammation** in RA patients." (Brown at p. 5383, 2nd column, emphasis added.)

For example, the accumulation of uric acid crystals in the joints causes pain and inflammation **through stimulation of TNFα release**. See, e.g., F. S. di Giovine et al., J Clin Invest (1991) 87:1375-81.

In the case of osteoarthritis, it should be noted that cartilage is a living tissue that is continuously maintained and remodeled by chondrocytes. Osteoarthritis is believed to result from

degradation of cartilage by dysregulated chondrocytes. See, e.g., S.R. Goldring et al., Clin Orthop (2004) 427S:S27-36:

> "Chondrocytes are responsible for maintaining the structural and functional properties of the extracellular matrix components of adult articular cartilage. These cells remodel their extracellular matrix through catabolic and anabolic mechanisms that under physiologic conditions are maintained in a state of equilibrium. In OA the balance between synthetic and degradative activities are uncoupled and this results in a loss of cartilage matrix components and alterations in the composition and structural and functional properties of the articular cartilage. * * * Although investigators have used cartilage and isolated chondrocytes from different sources, the results are remarkably consistent, suggesting that **proinflammatory cytokines such as IL-1 and TNF-α contribute to the dysregulation of chondrocyte function that leads to the progressive degradation of the cartilage matrix and loss of joint function.**" (Goldring et al. at p. S31, second column, emphasis added.)

The ultimate cause of SLE is unknown, but this is not true of the mechanism of pathology. SLE is characterized by the presence of auto-antibodies that attack tissues and cause inflammation that leads to tissue damage. See, e.g., M. Aringer et al., Arth Rheum (2004) 50(10):3161-69:

> "Tumor necrosis factor (TNF) is an important proinflammatory cytokine with pleiotropic properties [cites omitted], including the activation of a cascade of inflammatory events that lead to tissue destruction [cites omitted]. In most studies, TNF is found to be markedly increased and appears to be bioactive in the sera of patients with active SLE, and levels of TNF have been shown to correlate with SLE disease activity [cites omitted]." (Aringer et al. at p. 3162, first column.)
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> "This study was primarily designed as a first open trial to examine the safety of infliximab in SLE and not to prove its efficacy. However, the observed clinical findings under TNF blockade suggest that infliximab may have a therapeutic effect in patients with SLE." (Aringer et al. at p. 3167, first column.)
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> ""However, small open trials have provided important clinical information that has led the way to infliximab therapy in rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis [cites omitted], and similar trials in SLE have laid the groundwork for subsequent clinical trials [cite omitted]." (Aringer et al. at p. 3167, second column.)

Although infliximab is a chimeric anti-TNFα antibody, the implication of TNFα in SLE (and RA, ankylosing spondylitis, and psoriatic arthritis) is clear, as is the utility of inhibiting TNFα activity and/or release.

As with the various forms of arthritis, ARDS also has a number of different precipitating causes. However, ARDS is characterized by a local inflammatory response in the lung (see, e.g., M.

Bhatia et al., J Pathol (2004) 202:145-56 at p. 146, first column). Again, TNF-α (and IL-1β) is believed to mediate the inflammation and subsequent tissue damage:

> "Both TNF-α and IL-1β are present in the bronchoalveolar lavage fluid of patients at risk for ARDS and with established ARDS [cites omitted]. The highest concentrations of TNF-α and IL-1β occur in the bronchoalveolar lavage fluid from patients with sustained ARDS. The ratios of bronchoalveolar lavage fluid to serum cytokine concentrations are typically elevated, suggesting a pulmonary origin [cites omitted]." (M. Bhatia et al. at pp. 146-47.)

See also D. Yoshinari et al., Crit Care Med (2001) 29(3):628-34, reporting the treatment of ARDS in an animal model with a p38 MAP kinase inhibitor.

Applicants thus submit that the specification is in fact enabling for the scope of the claims, and that the rejection is thus overcome.

B. Claims 25-26

Claims 25-26 were rejected under §112, first paragraph, as not enabled for the treatment of restenosis or cancer. Applicants respectfully traverse.

Applicants submit that, as with the treatment of arthritis above, angiogenesis and restenosis are treated with p38 kinase inhibitors of the invention by inhibition of FGFR activity. However, Applicants have amended claim 25 above to limit it to the treatment of atherosclerosis (canceling claim 26), and intend to pursue the canceled subject matter in a co-pending application.

C. Claims 22 and 24

Claims 22 and 24 were rejected under §112, first paragraph, as not enabled for the treatment of Alzheimer's disease ("AD"). Applicants respectfully traverse.

The mechanism cited by the Examiner for the pathology of AD does not constitute a complete description of the disease. The fact that AD can be treated with acetylcholinesterase inhibitors does not mean that only such compounds will ever be effective. For example, if AD is caused by insufficient acetylcholine, or excessive glutamate, why does insufficient acetylcholine or excessive glutamate occur in the brains of AD patients, but not others? In fact, AD is now thought to be a chronic inflammatory disease, treatable with p38 inhibitors. See, e.g., T. Müller, Curr Opin Invest Drugs (2002) 3(12):1763-67 at p. 1764, second column, describing p38 inhibitor CPI-1189 in

clinical trials for Alzheimer's disease, Parkinson's disease, HIV-associated dementia, and multiple sclerosis.

Accordingly, Applicants submit that the use of p38 inhibitors, such as the compounds of the invention, is credible and substantial, and that the claims are thus enabled.

Rejection Under §112, Second paragraph

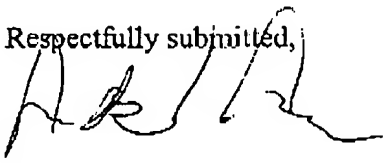
Claims 22-26 were rejected as indefinite under §112, second paragraph. Applicants respectfully traverse.

Claim 22 was rejected for recitation of a "p38 MAP kinase mediated disorder", on the assertion that this is indefinite. Applicants respectfully traverse: p38 mediated disorders" are defined in the specification at page 23, lines 14-19, and page 25, lines 1-5 (paragraph [100]), and include those diseases or disorders that are mediated by the release of IL-1, IL-6, IL-8, TNF-α, and the like. Most of the known diseases included in this definition are believed to be listed in the specification at page 23, line 20 through page 24, line 19. As noted by the Examiner, any particular drug may or may not be effective in an individual patient or subject, for example due to individual differences in distribution or metabolism; thus, the definition of "p38 mediated disorder" does not depend on an individual's reaction to a particular compound. A "p38 mediated disorder" is determined by the involvement of p38 in the etiologic process of the disease, a fact which can be determined, for example, by measuring the levels of IL-1 and TNF-α in the subject.

Claim 25 was rejected for recitation of "FGFR kinase mediated disorders". Applicants submit that this rejection is moot in view of the limitation of claim 25 to atherosclerosis.

Applicant respectfully submits that all rejections are thus overcome, and that the application is now in condition for allowance. Such action is solicited.

Respectfully submitted,



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